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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,759	01/30/2002	Adam Lerner	701586/50174-DIV	8480

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/060,759	LERNER, ADAM	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15* is/are allowed.

6)☒ Claim(s) *1-7 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 4/25/2008, are acknowledged and entered. Claims 1-7 and 15-16 are pending and under examination.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 16 are again rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method comprising administering to a subject a therapeutically effective amount of an inhibitor that specifically inhibits Type 4 cyclic adenosine monophosphate phosphodiesterases.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a generic genus, *i.e.*, generic PDE4 inhibitors.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical

properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There are two species of the claimed genus disclosed that are within the scope of the claimed genus, *i.e.* rolipram and XX5 (page 5, lines 2-9). The disclosure of a single disclosed species (or two species) may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompass numerous species that are not further described.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a generic genus of inhibitor compounds, *i.e.*, inhibitors of Type 4 PDE purported to have anticancer activity. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Applicant's arguments have been considered but are not persuasive. Applicant argues that the claimed class of compounds was a known class of compounds at the time the application

was filed, rather than an unknown class of compounds. Moreover, Applicant says that the pending claims are not directed to compounds per se but rather to methods for treating CLL using specific PDE4 inhibitors. However, virtually any compound claim could be transformed into a method claim simply by means of wording the claim in terms of a method of using the compound. Thus, this is little more than a semantic distinction without a difference. The claimed method *depends* upon finding compounds that selectively inhibit PDE4 activity. Without such compounds, it is impossible to practice the claimed method of treatment. The Declaration of Dr. Lerner filed 4/25/2008 has been considered. In said Declaration, Dr. Lerner states that a number of other *specific* PDE4 inhibitors were well known to the skilled artisan, such as RP73401, LAS31025, SB207499, CDP840, CP80633, CP77059, BRL61063, denbufylline, and MNS949. However, the fact that other PDE4 inhibitors might have been known is not probative of the present rejection, because the instant claims require inhibitors that *specifically* inhibit Type 4 cyclic adenosine monophosphate phosphodiesterases. By Applicant's definition, these inhibitors inhibit Type 4 but **not** Type 1 or 3 phosphodiesterases. Applicant also states that background level inhibition of Type 1 or 3 phosphodiesterases is permitted within the definition but where the inhibitor inhibits Type 4 as well as Type 1 and/or 3, but inhibits Type 4 to a greater extent (the amounts being subject to quantitative determination by assays described herein), the phrase "preferentially inhibits Type 4 phosphodiesterases" is used herein (as distinct from "Type 4 specific"). Thus, it appears that the claimed inhibitors that *specifically* inhibit Type 4 cyclic adenosine monophosphate phosphodiesterases cannot inhibit Type 1 or Type 3 cyclic adenosine monophosphate phosphodiesterases to a greater extent than Type 4 (Applicant does not define what "background level inhibition" means). No evidence has been submitted that the "PDE4 inhibitors" known in the art do not inhibit Type 1 or Type 3 PDEs at all or only have background level inhibition of such enzymes as required by Applicant's definition of compounds that "*specifically* inhibit Type 4 cyclic adenosine monophosphate phosphodiesterases" as opposed to compounds that *preferentially* inhibit Type 4 phosphodiesterases. Thus, while PDE4 inhibitors appear to be known in the art (i.e., inhibitors that inhibit PDE4), "specific" PDE4 inhibitors as defined by Applicant (i.e., those inhibitors that inhibit PDE4 but not PDE1 or PDE3) are not well known in the art as asserted by Applicant. Even those PDE4 inhibitors listed in the cited Teixeira et al. reference are only referred to as

"PDE4 inhibitors". There is no teaching that the listed inhibitors are "specific" to PDE4 as defined by Applicant.

Accordingly, the claims are deemed properly rejected as lacking written description for the claimed inhibitors that specifically inhibit Type 4 cyclic adenosine monophosphate phosphodiesterases as defined by Applicant in the specification.

Claims 1-7 and 16 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating CLL with rolipram or XX5, does not reasonably provide enablement for treating CLL in a patient with other inhibitors of Type 4 adenosine monophosphate phosphodiesterase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

The nature of the invention: The invention relates to the treatment of chronic lymphocytic leukemia comprising administering a specific inhibitor of Type 4 adenosine monophosphate phosphodiesterase.

Relative skill of those in the art: The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

State and predictability of the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively

unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a broad genus of compounds being used to treat the same cancer.

The breadth of the claims: The claims are extremely broad insofar as they disclose the treatment of chronic lymphocytic leukemia with a genus of compounds that is only defined with respect to its *in vitro* activity (*i.e.*, specific inhibition of Type 4 PDE).

The amount of direction or guidance provided and the presence or absence of working examples: The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat CLL with the broad genus of compounds contemplated by the claims, particularly in humans. The direction concerning treating cancer is found in the specification at pages 15-23, which provides cellular assays for determining the cell growth inhibitory effect of the claimed compounds. Only rolipram and XX5 were actually tested in these assays. Applicant describes formulations at pages 7-11. No doses required to practice the invention are described. Since

rolipram and XX5 have only been demonstrated to induce apoptosis of CLL cells *in vitro*, how is the skilled physician to know what dose to use for each of the compounds contemplated for administration in the instant claims? There are no guidelines for determining the doses needed to treat CLL *via* enteral administration (claims 2-3) or parenteral administration (claim 4). There is an *in vitro* cellular assay for induction of apoptosis of CLL cells described in pages 15-23 but it is unclear if this assay correlates to the induction of apoptosis in such cells with any and all specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase as only rolipram was tested. There are no working examples of treatment of CLL in animals or man.

The quantity of experimentation necessary: Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the full scope of the instantly claimed genus of compounds (*i.e.*, specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase) could be predictably used as a treatment for CLL in human patients as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).
In the instant case, Applicant has presented a general idea that because rolipram and XX5 induce apoptosis of CLL cells in vitro, then all specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase must therefore, *a priori*, be useful in the treatment of CLL in human patients. However, the claims encompass a multitude of compounds, defined only by their inhibition of an enzyme, having a plethora of chemically and biologically distinct substituents.

It is evident that a very small percentage of the claimed compounds were actually tested (for induction of apoptosis *in vitro*) by Applicant and both of the tested compounds were already known in the art as specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase. Applicant has provided no means for the skilled artisan to synthesize and test other compounds for specific inhibition of Type 4 adenosine monophosphate phosphodiesterase. Further, inhibition of an enzyme *in vitro* is not generally predictive of such activity *in vivo* (due to

possible metabolic degradation of the active compound *in vivo*, limited bioavailability, etc.). Considering the broad scope of the claimed invention, it would take undue experimentation for the skilled artisan to synthesize and identify specific inhibitors of Type 4 adenosine monophosphate phosphodiesterase, determine whether such inhibitors are active *in vitro*, determine whether compounds active *in vitro* are active *in vivo*, and finally evaluate whether a compound active in an *in vivo* model of CLL is effective in the treatment of human patients.

Determining if any particular claimed compound would treat any particular cancerous disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Applicant's arguments have been considered but are not persuasive. Applicant argues that he has shown that five different PDE4 inhibitors are effective in treating CLL (Declaration of Dr. Lerner filed 4/25/2008). However, no where has Applicant demonstrated any *in vivo* activity against CLL as presently claimed (i.e., "treating a patient"). All the data that has been presented relates to in vitro cell apoptosis or augmentation of glucocorticoid receptor in B cell CLL. While in vitro models are certainly important in the development of anticancer drugs, the fact that a particular compound induces apoptosis of CLL cells in a petri dish does not, a priori, mean that the same compound will be therapeutically effective in treating CLL in a patient. As such, given the broad scope of the claims, which encompass treating a patient having CLL with any and all specific inhibitors of PDE4, it would take undue experimentation to determine what PDE4 inhibitors, out of all PDE4 that might exist in the art, are therapeutically effective in the treatment of CLL. In fact, Cooper et al. (1999) cited by Applicant as Exhibit C in the Declaration filed 4/25/2008, teaches that *in vitro* PDE4 activity "does not predict *in vivo* efficacy" in an experimental model of eosonophil trafficking. As such, given the unpredictability of treating cancer in patients, coupled to the fact that *in vitro* PDE4 activity does not necessarily correlate to *in vivo* PDE4 activity, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed

invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/

Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614